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EXAMINER	
DEJONG, ERIC S	

ART UNIT	PAPER NUMBER
1631	

DATE MAILED: 07/11/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/611,823	UCHIDA, KIYOSHI	
	Examiner	Art Unit	
	Eric S. DeJong	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 April 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *8-25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED OFFICE ACTION

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 11-17 and 19-25 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

Claims 11 and 19 each recite the limitation of "said numerical value is expressed as "$((L+1)/r)^F \cdot \exp(|\Delta G|/RT)$" and further define the term "r" as "one plus the number of nucleic acid bases between said first target region and said complementary region". Upon review of the instant specification it is clear that applicant has contemplated the use of the above described numerical expression for use in the instantly claimed methods. However, no clear support has been found for the claimed term "r" being equated to at "one plus the number of nucleic acid bases between said first target region and said complementary region" as defined in claims 11 and 19.

Page 12, lines 9 and 10 of the instant specification provides one definition of the term "r" as the "...distance between one of double strands and another strand (number

of bases between 2 chains (regions) +1)." The terminology used in this definition is inconsistent with the terminology recited in the instant claims, which recite "a first and second single stranded sequences identified in within a target sequence of mRNA". While this definition does provide for adding 1 to a number of bases between 2 chains, it cannot be determined if the terminology used in the disclosure is coextensive in scope with the instantly claimed definition for "r" in claims 11 and 19.

In contrast to the above described definition from the specification, a second definition for the claimed term "r" [provided on page 21, lines 6-8 of the disclosure] states that "...r is expressed as the distance (in terms of number of bases) between the nearest sites in the substantially complementary chain regions. However this definition also does not provide sufficient support for the instantly claimed definition of "r" as it does not disclose adding 1 to the number of bases defining the distance between nearest sites in complimentary regions.

Therefore, the recited definition of the term "r" in instant claims 11 and 19 represents NEW MATTER. Claims 12-17 and 20-25 are also included under this rejection due to their dependence from either claim 11 or 19.

For the benefit of applicant, it is acknowledged that the disclosure does provide sufficient antecedent basis for the claimed term "r" being defined as --an integer representing the number of nucleic acid bases between a first target region and a complementary region--. As such, an amendment to claims 11 and 19 containing the above definition for the term "r" would be sufficient to overcome the above described NEW MATTER rejection.

Claims 8-25 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In In re Wands (8 USPQ2d 1400 (CAFC 1988)) the CAFC considered the issue of enablement in molecular biology. The CAFC summarized eight factors to be considered in a determination of "undue experimentation." These factors include: (a) the quantity of experimentation necessary; (b) the amount of direction or guidance presented; (c) the presence or absence of working examples; (d) the nature of the invention; (e) the state of the prior art; (f) the relative skill of those in the art; (g) the predictability of the art; and (h) the breadth of the claims.

In considering the factors for the instant claims:

a) In order to use the claimed invention one of skill in the art must assign the numerical values from either step (c) of independent claim 8 or step (h) of independent claim 18 to each nucleotide within all selected pairs of complementary sequences. In performing either step, every nucleotide within said sequences would be assigned the same numerical value and therefore be rendered indistinguishable. For the reasons discussed below, there would be an unpredictable amount of experimentation required to practice the claimed invention. *See also the rejection under 35 USC § 112, second paragraph discussed below.*

b) The disclosure describes methods of designing antisense oligonucleotide

sequences wherein each nucleotide of each selected sequence pair is assigned different numerical values determined on the basis of distance between a pair of complimentary sequences and the bond energy ΔG for each individual sequence selected from all possible pairs of complimentary sequences within a target mRNA or precursor. The disclosure does not describe a method wherein each nucleotide of each selected sequence pair is assigned the same numerical value.

c) The disclosure provides working examples of designing antisense oligonucleotide sequences wherein each nucleotide of a selected sequence pair is assigned different numerical values on the basis of distance between a pair of complimentary sequences and the bond energy ΔG for each individual sequence selected from all possible pairs of complimentary sequences within a target mRNA or precursor. The disclosure does not provide working examples of designing antisense oligonucleotides wherein each nucleotide of every selected sequence pair is assigned the same numerical value.

d) The nature of the invention, designing antisense oligonucleotide sequences on the basis of distance between a pair of complimentary sequences and the bond energy ΔG for each individual sequence selected from all possible pairs of complimentary sequences within a target mRNA, is complex.

e) The prior art does not provide working examples of designing antisense oligonucleotides wherein each nucleotide of every selected sequence pair within a given mRNA target is assigned the same numerical value.

f) The skill of those in the art of designing antisense oligonucleotide sequences is

high.

g) The predictability of designing antisense oligonucleotide sequences on the basis of a distance between a pair of complimentary sequences and the related bond energy, ΔG, is known in the prior art.

h) The claims are narrowly defined in that each nucleotide of the selected pairs of complementary sequences are assigned the same numerical values.

In practicing the claimed invention, the skilled practitioner would be required to assign the same numerical values to every nucleotide within all selected pairs of complementary sequences. In so doing, all selected pairs of complementary sequences would be indistinguishable on the basis of a summation of the numerical values assigned to the nucleotides contained therein. In this event, the skilled practitioner would first turn to the instant description for guidance in using the claimed invention. However, the description lacks clear evidence how such indistinguishable sequences could be further differentiated so as to select one or more regions that have a low summed value relative to another. Therefore, the skilled practitioner would turn to the prior art for such guidance, however the prior art does not discuss how to further differentiate such antisense oligonucleotide sequences. Finally, said practitioner would turn to trial and error experimentation to determine a relationship between said sequences. Such amounts to undue experimentation.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> **The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.**

Claims 8-25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 8 recites the limitation of "selecting all pairs of sequences on the target mRNA, or its precursor,... without independently selecting pairs of sequences that are shorter than, and composed of nucleotides of, the selected sequences" (see lines 3-6 of the instant claim). In practicing this step, the resultant "all selected pairs" must exclude pairs of sequences which are shorter than the selected sequence. This limitation appears to contradict itself, as it is unclear how a pair of selected complimentary sequences from within a target mRNA or its precursor could ever be "shorter than the selected sequences". As such, the instant limitation relies on circular logic as a practitioner is required to know what the selected sequences are without ever first defining or identifying all pairs of selected sequences.

Further, it is unclear from the above limitation if all pairs of sequences are selected only from either the target mRNA or the precursor sequence, or, alternatively, if the instant limitation is open to complementary pairs of sequences from selected from both a target sequence and its precursor simultaneously.

Claims 9-17 are also included under this rejection due to their dependence from claim 8.

For the purpose of continuing examiner, the Examiner has construed that the above described step (a) of instant claim 8 reads on selecting all pairs of complimentary sequences from with the target mRNA or its precursor that are separated by at least three nucleotides.

Claims 8 and 18 recite the limitations of "selecting one or more regions" and "relative to another region" as recited in steps (e) and (f) of claim 8 and in steps (l) and (m) of claim 18. It is unclear from the instant claims whether the recitation of terms "region" and "regions" relate to specific portions of some or all of the complementary sequences derived from the target mRNA, or its precursor, utilized in the previously recited method steps or if the claimed terms are intended to encompass other "regions" of a sequence consisting of at least 6 contiguous nucleotides. If applicants intend the terms "region" and "regions" to specifically refer to portions of the mRNA target sequence selected in the preceding method steps, then the claimed limitations of "region" and "regions" further lack proper antecedent basis in the instant claim. Claims 9-17, and 19-25 are also included under this due to their dependence from either of claims 8 or 18.

For the purpose of continuing examination, the Examiner has construed the claimed limitations of a "region" and "regions" to read as one or more sequences found within the target mRNA sequence or its precursor as recited in steps (a) of claim 8 and steps (a) and (b) of claim 18.

Response to Arguments

Applicant's arguments filed 04/26/2006 have been fully considered but they are not persuasive.

In response to the rejection of claims under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement, applicants argue that the definition of "r" as defined in amended claims 11 and 19 are fully supported by the specification. Applicants further point to example on page 21, line 6-8 and page 23, lines 4-9 of examples calculation that provide support for the use of $r \geq L+1$.

In response, it is noted that the basis of the instant rejection is that the disclosure does not provide clear support for the claimed term "r" being equated to "one plus the number of nucleic acid bases between said first target region and said complementary region" (see lines 4 and 5 of claim 11 and lines 4 and 5 of claim 19). However, applicants argue (page 8, lines 8-10 of applicants response filed, filed 04/26/2006) that the term is properly defined as "...'r' is calculated as the numerical position of the first nucleotide of the second sequence in the duplex (43) minus the numerical position of the last nucleotide of the first sequence involved in the duplex." Since the instant claim recites a different definition for the term "r" than that argued by applicants, applicants argument is not found persuasive in regards to providing support for the instantly claimed subject matter.

In regards to the rejection of claims under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement, applicants argue that once an mRNA

sequence is analyzed fully as specified by the instant claims, the same numerical values are not assigned to every nucleotide within all selected pairs of complementary sequences (see page 9, lines 7-12 of applicants response). Applicants further provide a sample calculation wherein a different number is assigned selected pairs of an RNA sequence.

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., that the same numerical values are not assigned to every nucleotide within all selected pairs) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). In the instant case, claims 8 and 18 each recite "assigning a numerical value to said sequences" (see claim 8, line 7 and claim 18, line 15), and as such is limited to assigning a number, rather than a plurality of different numbers, to selected sequence pairs, as argued by applicants. Further, steps (b) of claim 8 (g) of claim 18 do not recite any limitation wherein values are assigned to a given sequence are further assigned to each nucleotide within the sequence. As such, the significance of subsequent steps (c) of claim 8 and step (h) of claim 18, which recite "assigning the numerical values... to each nucleotide of each of the paired sequences", is not apparent since the values that are assigned to a nucleotide reflects bond energy ΔG for an entire sequence, rather than an energy reflecting some property of an individual nucleotide. Regarding the example of practicing the claimed invention presented by applicants (see page 9, lines

7-12 of applicants response), applicants example lacks any step wherein any numerical values were assigned to each nucleotide of the paired sequences that reflect bond energy, as required by steps (b) and (c) of claim 8 and steps (g) and (h) of claim 18. Rather, the values that are assigned to individual nucleotides in the example are only related to the nucleotides position. As such applicants example representative of practicing the instantly claimed methods.

In regards to the rejection of claims under 35 U.S.C. § 112, second paragraph, as being indefinite, applicants argue that the rejection is mood in consideration of amendments made to claims 8 and 18. Applicants further argue that in selecting pairs of sequences in the first step the longest sequence is selected, when evaluating the potential complementarity of sequences the longest possible region of sequence is considered, and that a pair of sequence would not be independently selected because the sequences are both in the initial duplexed sequences and shorter than the initial duplexed sequences. Applicants further site support from page 6, lines 7-23 of the instant specification.

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., selecting pairs of sequences in the first step the longest sequence is selected, considering the longest sequence in evaluating potential complementarity, and duplexed sequences) are not recited in the rejected claims. Although the claims are interpreted in light of the specification, limitations from the specification are not read into

the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Further, the amendments made to the instant claims do not resolve the above discussed issue where it is unclear from the above limitation if all pairs of sequences are selected only from either the target mRNA or the precursor sequence, or, alternatively, if the instant limitation is open to complementary pairs of sequences from selected from both a target sequence and its precursor simultaneously.

In regards to the rejection of claims 8-17 under 35 USC §112, second paragraph, for being indefinite, applicants argue that the terms "region" or "regions" as recited in steps (e) and (f) of claim 8 and in steps (l) and (m) of claim 18 are not the sequences recited in steps (a) of claim 8 and in steps (s) and (b) of claim 18. Applicants further argue that the terms "region" or "regions" as referred to in steps (e) and (f) of claim 8 and steps (l) and (m) of claim 18 are selected from data calculated from the numerical values assigned to the "regions" of the previously determined sequences.

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., selected from data calculated from the numerical values assigned to the "regions") are not recited in the rejected claims. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). The neither the instant claims nor the specification provide a definition for the terms "region" or "regions" that would limit the scope of the terms as recited instant claims. As such, the instant claims

remain unclear as they still encompass other "regions" of other sequences consisting of at least 6 contiguous nucleotides.

Further applicants argument does not address the antecedent basis issue that would be present in the claim, if claims were amended to limit the terms "region" and "regions" to referring to portions of the mRNA target sequence, or precursor thereof, selected in the preceding method steps. Specifically, the limitations of "region" and "regions" would lack proper antecedent basis in the instant claim.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eric S. DeJong whose telephone number is (571) 272-6099. The examiner can normally be reached on 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (571) 272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

EDJ EDJ

28 June 2006

JOHN S. BRUSCA, PH.D
PRIMARY EXAMINER